TOWARDS ORGANIC SYNTHESIS IN MICROFLUIDIC DEVICES: MULTICOMPONENT REACTIONS FOR THE CONSTRUCTION OF COMPOUND LIBRARIES

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Abstract

A silicon-machined micromixer[1] has been coupled with electrospray ionisation mass spectrometry (ESI-MS) as a step toward the development of a μSYNTAS (miniaturised-SYNthesis and Total Analysis System).[2] The micromixer has been successfully used for the synthesis of small organic molecules *via* C-C and C-N bond-forming steps. The potential utility of this device for the production of compound libraries is demonstrated through a multicomponent reaction, thus illustrating a possible methodology for combinatorial synthesis.

Keywords: **μSYNTAS, micromixer, multicomponent reaction, combinatorial**

1. Introduction

The automation of compound library synthesis and analysis is an area of great interest, especially within the pharmaceutical industry. Combinatorial synthesis, for example, using bead, 'tea-bag' or multipin technologies have become highly developed in recent years.[3] Nevertheless, current combinatorial methods based on solid-support technologies feature inherent shortcomings when attempts are made to transfer them to a μSYNTAS:

- additional steps such as reagent *attachment* (to the support) or product *detachment* (for subsequent analysis) are required;
- alternative technologies must be developed for the *in situ* analysis of compound libraries;
- possible - and often unpredictable - influence of solid support over reaction chemistry.

Consequently, our development of a microfluidic device for the on-line synthesis and analysis of chemically- or pharmaceutically-relevant intermediates in a *solution-phase* system is of fundamental significance for the elaboration of a μSYNTAS.

2. Theory

The principle of *distributive* mixing[5] was the fundamental concept behind the design of the micromixing device. The mixing of liquids in a microengineered system generally falls into the regime of laminar flow where viscous forces dominate over inertia and dampen out any irregularity in the flow pattern. Under these conditions, diffusion is the only mechanism for

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the transfer of molecules (*i.e.* reagents) across the boundaries of adjacent fluid domains. The glass/silicon micromixer physically splits the fluid streams into smaller segments and redistributes them in such a way that the striation thickness is significantly reduced; this is achieved by changes in the geometry of the flow-channels (**Figure 1**).[1] Consequently, accelerated diffusion between adjacent domains occurs, leading to a homogeneous mixture at the molecular level. This provides ideal conditions for diffusion-controlled reaction chemistries to take place.

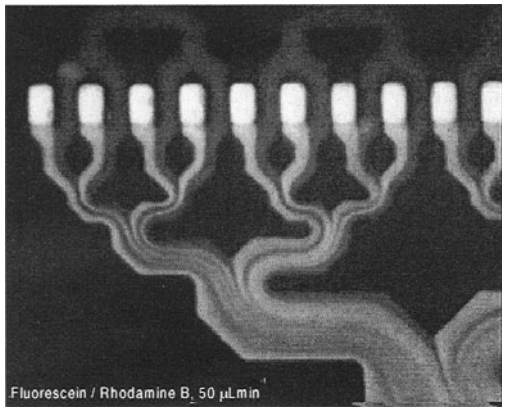
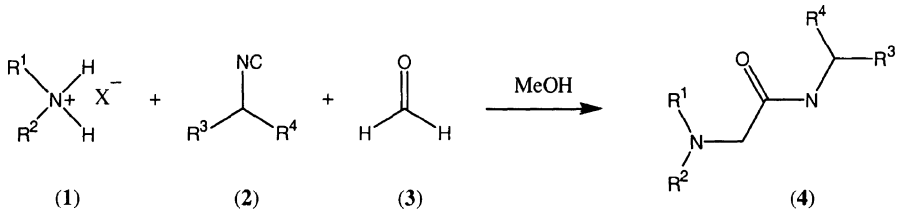


Figure 1 Visualisation of on-chip laminar flow

In order to assess the potential of this device as a platform for chemical synthesis, and to investigate the influence of the micromixer environment over the progress of reaction chemistries, the multicomponent reaction (MCR) between a secondary amine salt (**1**), an isocyanide (**2**) and formaldehyde (**3**) was performed (**Scheme 1**).[4] This particular reaction is 'highly exothermic' in nature and is conventionally performed at 0°C under 'bench-top' conditions to provide an α-dialkylacetamide (**4**).



Scheme 1 Ugi multicomponent reaction (MCR)[4]

3. Experimental

The micromixer was coupled to an electrospray ionisation mass spectrometer (ESI-MS) using fused silica capillaries to connect the chip to a standard electrospray unit (4 kV potential) (**Figure 2**). A solution of formaldehyde (2.0 mM) was infused through one of the inlets of the micromixer (5 $\mu Lmin^{-1}$) and pure solvent infused through the other inlet (5 $\mu Lmin^{-1}$). A methanol solution of the remaining MCR components [isocyanide (2.0 mM):amine salt (0.2 mM)] was then infused in place of the pure solvent-flow while observing the output of the ESI-MS. All procedures were carried out at room temperature. Scans were made at a rate of 1 Hz between 90 and 1000 *m/z* units. The total outlet flow from the chip was then analysed on-line by the ESI-MS with *no purification steps*.

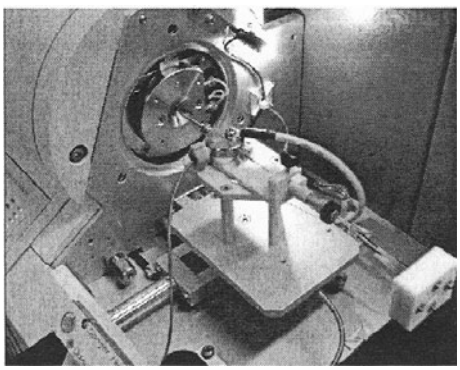


Figure 2 On-line coupling of the micromixer to Perseptive Biosystems Mariner TOF-MS

4. Results and discussion

The mass spectrum for the reaction performed with the micromixer under the described conditions is shown (**Figure 3**). A significant peak for the parent ion of the expected product is observed with m/z = 225 $[M + H]^+$. The fact that the desired product is obtained at room temperature is extremely interesting, since the traditional 'bench-top' approach (round-bottom flask, stirrer bar, 5-10 mL solvent volumes) requires reduced temperatures for the product to be obtained.[4]

The geometry of the micromixer (channel surface area *vs.* channel volume) and the resultant capacity for rapid dissipation of heat produced within the channels is presumably the source of this phenomenon. The observation of this effect has implications for the transfer of reactions to microscale devices for which elevated or reduced temperatures are usually required.

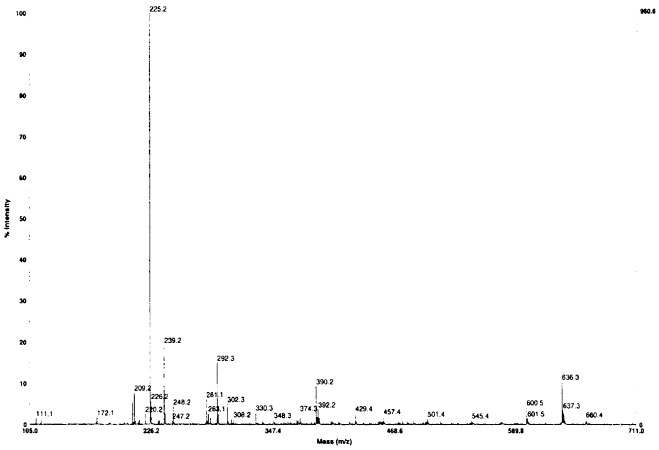


Figure 3 The mass spectrum of a continuous-infusion MCR

5. Conclusions

A micromachined mixing device has been demonstrated as an effective reaction platform for a multicomponent reaction (MCR) providing a possible route towards combinatorial chemistries on a μSYNTAS.

Acknowledgements

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